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INTERNATIONAL APPLICATION PUBLISH

WO 9604067A1

(51) International Patent Classification 6 :

B01D 61/00, G01N 33/48

A1

(11) International Publication Number:

WO 96/04067

(43) International Publication Date:

15 February 1996 (15.02.96)

(21) International Application Number: PCT/GB95/01834

(22) International Filing Date: 2 August 1995 (02.08.95)

(30) Priority Data:

9415560.3	2 August 1994 (02.08.94)	GB
9421682.7	27 October 1994 (27.10.94)	GB
9422870.7	12 November 1994 (12.11.94)	GB
9422875.6	12 November 1994 (12.11.94)	GB

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

**Published***With international search report.**Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

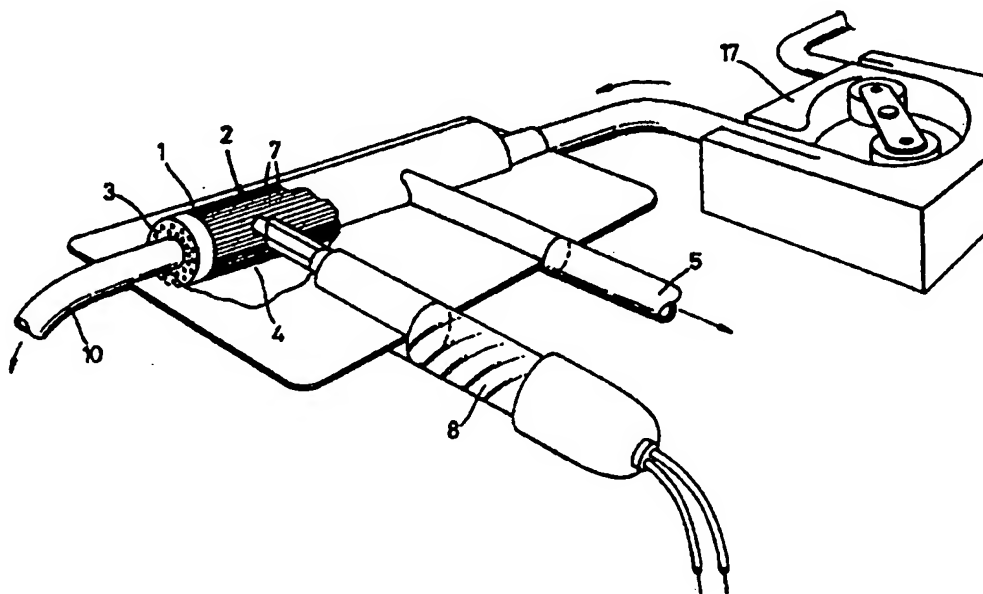
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(54) Title: MEMBRANE FILTER UNIT



(57) Abstract

The present invention describes a device to process a fluid, the device having a membrane filter, wherein an agent able to detect or cause modification of at least one component of said fluid is localised in said device, preferably on the membrane. The device is arranged to filter the fluid by cross-flow filtration. A preferred form of membrane filter is hollow fibre membrane(s), especially a single hollow fibre membrane. Space between the exterior of the membrane and the inside surface of the outer casing of the device may be completely or partially filled with a solid material, which may contain the agent.

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1     "Membrane Filter Unit"

2

3     This invention relates to the membrane units for  
4     filtration or analysis or to support cell culture.

5

6     It is known to control chemical and biological  
7     processes performed in process vessels by withdrawing  
8     samples, filtering the samples to remove undissolved,  
9     colloidal or suspended particles or materials of high  
10    molecular weight and then subjecting the filtrate to  
11    chemical tests. The filtrate may optionally be  
12    returned to the mother liquor after analysis. The  
13    whole operation may be time consuming and laborious and  
14    the quantities of filtrate removed may affect the  
15    course of the chemical or biological process.  
16    Alternative analytical methods that are available for  
17    "real-time" analysis within the process vessel are  
18    often highly specific to the particular analyte,  
19    provide only very restricted information and may be  
20    expensive.

21

22    It would be advantageous to have a system that allowed  
23    continuous sampling without causing substantial change  
24    to the total volume of the process liquor, but which

1 automatically removed substances over a chosen particle  
2 size or over a chosen molecular weight by filtration,  
3 and returned the filtrate to the process liquor. It  
4 would be especially advantageous if the system involved  
5 the temporary removal of only a minimal amount of the  
6 process liquor from the process vessel.

7  
8 Additionally many process liquors contain soluble or  
9 dispersed ingredients which require to be separated,  
10 combined, monitored, analysed or controlled. These  
11 ingredients may be reactants, intermediates or products  
12 of the process. However, analysis and/or control are  
13 frequently made difficult, or even impossible, by the  
14 presence of substances in suspension or of substances  
15 of lower or higher concentrations in solution. The  
16 problems which arise because of the presence of these  
17 substances include obstruction of the membrane pores,  
18 discoloration or turbidity of the liquor making  
19 colorimetric analysis difficult, and chemical  
20 imbalances which make analysis and processing  
21 difficult, and contamination, which can lead to the  
22 rapid deterioration of, for example, cells and/or  
23 sensor elements. Micro- and ultra-filtration membranes  
24 exist which allow the separation of particles such as  
25 proteins, cells, cell debris and bacteria, from one  
26 another, but separation of these materials or  
27 substances from one another can be difficult,  
28 inconsistent and time consuming. The delay in the  
29 response time may be unacceptable.

30  
31 The above also applies where it is desired to grow  
32 cells in culture on a membrane or other support and  
33 where the cells or a sample thereof are to be exposed  
34 to challenge substances.

35  
36 The present invention provides a device to process a

1 fluid, the device having a membrane filter, wherein an  
2 agent able to detect or cause modification of at least  
3 one component of said fluid is localised in said  
4 device, for example is located on or in proximity to  
5 said filter.

6  
7 The device of the invention is arranged so that  
8 filtration of the fluid occurs by cross-filtration, ie  
9 the fluid to be processed flows along the surface of  
10 the membrane and is not directed perpendicularly  
11 towards the membrane.

12  
13 In a preferred embodiment the device of the invention  
14 comprises an agent (sensor) able to detect a component  
15 in the process liquor, which may be, for example,  
16 located in the test fluid.

17  
18 Optionally, the detected or modified component is  
19 released back into the fluid.

20  
21 The fluid to be processed may comprise a liquid  
22 (optionally including dissolved or suspended solid  
23 particles). Optionally the fluid to be processed  
24 comprises a gas. Alternatively the fluid to be  
25 processed is a liquid suspension of cells or parts of  
26 cells.

27  
28 In one embodiment, the device of the invention is for  
29 use in a continual processing operation, that is to say  
30 a constant supply of the liquid to be processed flows  
31 through the device. In this embodiment it is preferred  
32 that the agent is self-regenerating, although it may  
33 also be possible in certain circumstances for the agent  
34 to be artificially regenerated at intervals during the  
35 processing operation or even for the agent, optionally  
36 together with the filter on which the agent is located,

1 to be replaced periodically as required. It is  
2 possible for the device to be adapted to support cell  
3 growth on the membrane, the fluid flowing through the  
4 membrane comprising all of the nutrients needed to  
5 support cell growth. Such an arrangement provides a  
6 useful experimental tool as well as a means of  
7 culturing and challenging cells to provide an in vitro  
8 diagnosis, for example by subsequent exposure of the  
9 cells to antibodies or other challenge substances.  
10  
11 In an alternative embodiment, the device of the  
12 invention is arranged for single use applications, such  
13 as testing body fluids eg blood, plasma, urine,  
14 synovial fluid and the like. Generally the device will  
15 be wholly disposable or will be partially disposable  
16 for such applications.  
17  
18 Optionally, the membrane may be selected to filter out  
19 a particular molecular size range so that only  
20 molecules below a certain size are present in the  
21 filtrate. The agent may be located on the post-  
22 filtration side of the filter where the agent to be  
23 modified is present in the filtrate. Alternatively the  
24 agent may be located on the pre-filtration side of the  
25 filter.  
26  
27 The agent may be located on the filter membrane by any  
28 convenient means, for example hydrophobic or  
29 hydrophilic attraction with the membrane surface or  
30 chemical bonding, such as ionic or covalent bonds.  
31 Hydrophobic attachment of the agent may be particularly  
32 required for certain embodiments, such as devices known  
33 as "electronic noses" which detect the presence and/or  
34 concentration of a gas. Preferably, the agent is  
35 physically attached to the membrane, advantageously by  
36 means of a covalent bond. It may be desirable for

1 certain agents to be attached to the membrane surface  
2 via a spacer molecule so that presentation of the agent  
3 is enhanced and/or that steric interference is reduced  
4 or avoided.

5  
6 Optionally more than one agent may be located on the  
7 same filter and these agents may act independently of  
8 each other on different substrates or may compete for  
9 the same substrate. Optionally two or more agents may  
10 sequentially modify the same original substrate. Thus  
11 the first agent acts on the unmodified substrate,  
12 producing an intermediate product. This intermediate  
13 product is then modified or detected by a second agent.  
14 A similar chain of reactions may be produced with any  
15 number of different agents.

16  
17 For certain applications the agent may be located on  
18 the walls of the chamber which collects the filtrate,  
19 or may be presented on beads, rods or the like located  
20 within the chamber collecting the filtrate. Likewise  
21 it is also possible for the agent to be similarly  
22 located on the filtrant (unfiltered) side of the  
23 membrane.

24  
25 It is possible for different fluids to be present on  
26 either side of the membrane, at least one of the fluids  
27 being subject to (positive or negative) pressure so  
28 that cross-filtration occurs. At least one component  
29 of one fluid is thus caused to move across the membrane  
30 and undergoes a chemical reaction with a component of  
31 the other fluid. The presence and/or amount of product  
32 may optionally be detected by a sensor.

33  
34 An example of this embodiment is the treatment of  
35 effluent containing at least one environmentally  
36 unacceptable component, which may be rendered harmless

1 via chemical reaction or which is to be measured. The  
2 required reactant is included in the fluid on the  
3 opposite membrane side. Either the reactant moves  
4 across the filter or, more preferably, the  
5 environmentally unacceptable component moves across the  
6 filter. The component may then either be subjected to  
7 a chemical reaction following which the end product  
8 thereof may either be discharged or collected  
9 separately or, if desired, recycled. Alternatively the  
10 component may be detected.

11  
12 The filtration device may use positive or negative  
13 pressure to control the ingress or egress of filtration  
14 fluid and/or the rate of filtration. The pressure may  
15 be reversible to allow "cleaning" of the membrane,  
16 extending their working life.

17  
18 Optionally the material to be sampled contains  
19 particulate matter such as cell debris or cells. In  
20 this situation the use of controlling pressure may be  
21 particularly useful. Where cells are present it may be  
22 desirable for the device to be a sealed unit so that  
23 the filtration process is totally contained within the  
24 filter cell.

25  
26 In one preferred embodiment the volume between one  
27 surface of a membrane and its boundary is at least  
28 partially filled with a material. The material may be  
29 either porous or non-porous depending on the intended  
30 use of the device and the membrane selected for use.  
31 Optionally, the volume defined between the membrane and  
32 the outer casing may be substantially filled with the  
33 material. Alternatively the material may fill separate  
34 portions of that volume, thus sub-dividing it into  
35 smaller discrete volumes. Suitable materials include  
36 polymers (for example polymeric adhesives), especially



1 light curable or UV curable polymers. Specific mention  
2 may be made of light or UV curable polymers available  
3 from Ablestick Ltd (for example LCM 32, LCM 34 and LCM  
4 35), Bostick Ltd or Dynax Inc (especially 191M) as  
5 being useful in this regard. Non-porous materials  
6 include solids through which parts of the filtrate can  
7 diffuse, for example gels (such as agar gels) or the  
8 like. The material may be introduced in liquid or  
9 semi-liquid form and solidified in situ. The presence  
10 of the porous material may enhance the speed of the  
11 response times in testing for the presence and/or  
12 amount of a test substance. The material may be chosen  
13 having regard to fluid in the filter cell and any test  
14 required.

15

16 As an example of this embodiment, a single hollow  
17 membrane fibre, or a bundle of such fibres, may be  
18 placed into an outer casing. The volume between the  
19 inner surface of the casing and the outer surface of  
20 the membrane fibre(s) may be filled with the material.  
21 The material may be inserted into that volume by  
22 injection and/or by capillary action. If required, the  
23 material may be cured, for example by exposure to blue  
24 light or to UV light. The mother liquor may then be  
25 fed down the material-filled volume, with the challenge  
26 or test substance being provided via the lumen of the  
27 membrane, or vice versa.

28

29 Alternatively, if a membrane in the form of a sheet is  
30 utilised, the material may fill at least part of the  
31 volume between a membrane surface and its boundary,  
32 normally the inner wall of the casing or a further  
33 membrane sheet.

34

35 Where a material is present in the manner described  
36 above, it is possible for the agent to be attached to,

1 contained within or encapsulated by the material.

2

3 In addition to a component-modifying agent located on  
4 the filter, the device of the present invention may  
5 optionally further comprise one or more detecting  
6 agents or sensors. The sensor(s) may, for example,  
7 monitor the level of modified component and optionally  
8 also the level of modified component. In a preferred  
9 embodiment the sensors are visually apparent or are  
10 arranged to give a visual display of their output (for  
11 example through a microprocessor or the like). Any  
12 commercially available sensor may be used in the  
13 apparatus of the present invention. Preferred examples  
14 include light-emitting, photo-reactive or  
15 photosensitive sensors.

16

17 Where the outer casing (and if present the material) is  
18 optically suitable, it will be possible to use  
19 colorimetric analysis to determine whether the test  
20 substance is present and/or the amount thereof.  
21 Desirably the presence of the test substance will be  
22 due to a colour change and it may be preferable in  
23 certain circumstances for the outer casing and/or  
24 material to be optically clear.

25

26 A component-modifying agent may be, for example, an  
27 enzyme, antibody, abzyme, a microbe (such as a bacteria  
28 or virus), genetic material (such as DNA or RNA),  
29 lectin, or any chemical reagent or catalyst, or any  
30 combination or functional part thereof. Generally  
31 where the agent is a biomolecule it will be attached  
32 covalently to the filter via a spacer unit, for example  
33 a carbon chain, optionally containing reactive groups,  
34 eg acrylic acid or acrylamide or the like. In this  
35 situation the agent is advantageously provided with any  
36 co-factor or co-enzyme necessary for modification of

1 the component in the liquid to be processed. The co-  
2 enzyme and/or co-factor may either be provided on the  
3 surface of the filter or may be included in the liquid  
4 being processed.

5

6 In a preferred embodiment the component of the liquid  
7 to be modified is a sugar and the agent is a sugar  
8 modifying enzyme, for example a saccharase.

9

10 Where the agent is a sugar modifying enzyme, preferably  
11 a sugar degrading enzyme (for example a saccharase),  
12 the device of the present invention is adapted to  
13 process sugar containing liquids, so that the sugar  
14 content of the processed liquid is altered, preferably  
15 is substantially reduced.

16

17 In one particular embodiment the component is a sugar.  
18 For example the component may be sucrose and the  
19 modifying agent may be sucrase and thus cause  
20 degradation of the sucrose into fructose and glucose.

21

22 In a further aspect, the present invention provides a  
23 process of detecting or modifying a component of a  
24 liquid substrate, wherein:

25

26 a. said liquid substrate is filtered by cross-flow  
27 filtration through a device as described above,  
28 the component being present in the filtrate; and

29

30 b. the filtered component is detected or modified by  
31 an agent located on a filter in said device.

32

33 Alternatively the agent may be located on the filtrate  
34 side of said filter.

35

36 Optionally said modified component is returned to the

1     filtrant of the liquid.

2

3     The membrane for use in the device of the invention may  
4     be of any convenient shape and mention may be made of  
5     hollow membrane fibres and flat sheet or tubular  
6     membranes. Hollow membrane fibres or bundles of such  
7     fibres may be preferred in certain situations since  
8     this form permits a relatively large surface area  
9     through which filtration may occur. For other  
10    applications, however, flat membrane sheets (or bundles  
11    of such sheets) may be preferable. The membranes may  
12    contain pores of sizes from 0.001 to 30 microns in  
13    diameter or alternatively may possess Molecular Weight  
14    cut-off values from, for example 100 to 1,000,000 (eg.  
15    300 to 100,000, 500 to 1,000) Daltons.

16

17    The membrane may be made of any convenient material and  
18    the present invention is not limited to the membrane to  
19    be used. Generally the membrane will be selected for  
20    the filtration size. Ceramic filters, for example, may  
21    filter particles of diameter 5.0  $\mu\text{m}$  to 0.1  $\mu\text{m}$  and  
22    hollow fibre membranes may filter molecules of 1 mDa to  
23    5 kDa in suitable membranes are available commercially  
24    and may be made of polysulphone, cellulose, cellulose  
25    diacetate, polypropylene, ceramics materials and/or  
26    other co-polymers.

27

28    The filtrate chamber may incorporate a sensor or  
29    plurality of sensors that produce electrical signals in  
30    response to changes in the chemical composition of the  
31    filtrate or of the fluid surrounding the sensor, and  
32    which sensors may be biosensors. Alternatively the  
33    device may comprise an agent able to modify one of the  
34    components of the fluid as described above.

35

36    The device may be adapted (optionally via a connector)

1 to form a close fit with syringe needles or syringe  
2 bodies. This arrangement may be particularly  
3 convenient where the sample to be tested is a  
4 biological fluid (eg blood, synovial fluid or the  
5 like). The syringe needle may itself be inserted into  
6 the device, for example where the membrane is a single  
7 hollow fibre the syringe needle may be inserted into  
8 the lumen of the hollow fibre. Alternatively the  
9 needle may be removed from the syringe and the neck of  
10 the syringe connected into the device. The syringe  
11 plunger may then be depressed, the fluid in the syringe  
12 being expelled into the device and undergoing cross-  
13 flow filtration followed by modification and/or  
14 detection. Thus, an extremely quick and simple test  
15 can be performed to give an "on-the-spot" diagnosis.

16

17 The device may be connected with pumps and tubing to  
18 form an apparatus arranged so that mother liquor may be  
19 continuously pumped through the device for separation  
20 and sampling; and in which apparatus there may be  
21 provision for returning the process liquor and/or  
22 filtrate to the mother liquor.

23

24 The flow through the membrane may be directionally  
25 reversible so that gel polarisation and/or cell  
26 attachment may be eliminated or substantially  
27 eliminated thus increasing the control and growth of  
28 cells and the operational life of the process system.  
29 Alternatively the flow rate may be reversed to increase  
30 the rate of reaction occurring at the membrane.

31

32 The device of the invention may have no vents to the  
33 atmosphere and may provide total containment for the  
34 fluids in process. The system may be constructed of  
35 materials that permit sterilisation of the system.

36

1 The device may in some embodiments have no vents to the  
2 atmosphere and provides total containment for the  
3 fluids being processed. The device may be constructed  
4 of materials that permit sterilisation of the system.

5

6 To ensure hydrophilicity of membranes, consisting of  
7 hydrophobic materials such as polypropylene, poly  
8 carbonate and hydrophobic polysulphone, one should  
9 follow the following general guidelines:

10

- 11 1. Use a solvent which wets the membrane and is  
12 soluble in water. Usually this is done by using  
13 96% ethanol solution.  
14
- 15 2. Fill up the module (ie the interior of the  
16 capillaries) with ethanol and keep them filled for  
17 at least 10 minutes.  
18
- 19 3. Replace the alcohol by water and apply reasonable  
20 transmembrane pressure (max. 1.0 Bar) to force the  
21 alcohol followed by water across the membrane.  
22 Maintain this condition for about 10 minutes. For  
23 a module with a membrane surface area of 1.0 m<sup>2</sup>  
24 one will require a minimum of 2 litres of water.  
25 Measure the flow rate of water.  
26
- 27 4. After performing the above steps the membrane  
28 should be ready for use.

29

30 In order to be able to use the hollow fibre membrane  
31 filters over a longer period of time one should follow  
32 the general cleaning procedure as outlined below:

33

- 34 1. After each filtration process rinse the hollow  
35 fibre membrane filter thoroughly with distilled  
36 water followed by an appropriate cleaning

- 1 solution: eg Decon-Neutracon Solution (neutral pH)  
2 for general cleaning of filters used for proteins  
3 and fatty substances. Rinse thoroughly afterwards  
4 with distilled water.  
5
- 6 2. The procedure should be followed by a rinsing  
7 procedure in water.  
8
- 9 3. The ceramic filters can be brushed after use to  
10 clean the surface of the filter, followed by a  
11 rinse procedure with appropriate cleaning  
12 solutions and distilled water.  
13
- 14 4. The hollow fibre membrane cartridges should be  
15 sterilised when applicable with the appropriate  
16 technique.  
17
- 18 5. The membranes should be kept wetted after use. In  
19 order to prevent the fibres from drying out, a 10-  
20 20% alcohol solution should be used for this  
21 purpose.  
22
- 23 One should follow the general guidelines for  
24 sterilising filters and other parts of the fluidlines  
25 that are in contact with the fluids which are to be  
26 processed. Details are to be found in the product  
27 guidelines for eg autoclaves and steam sterilisers  
28 supplied by various manufacturers. For those filters  
29 that will not withstand the higher temperatures as used  
30 for heat sterilising various chemical methods are  
31 available to sterilise the filters in a safe and  
32 efficient way.  
33
- 34 1. NaOH solution 4% (60 minutes). Not for use with  
35 cellulose or cellulose di-acetate filters.  
36

1     2.    Sterilising fluids for medical dialysing units  
2           such as Dialina and Renalin Acetoper.

3  
4     3.    Peractic acid 3%.

5  
6     4.    Formalin 4%.

7  
8     5.    Ethylene Oxide (up to 800mg/l).

9  
10    In one embodiment of the present invention there is  
11    provided a device having a filter cell of low internal  
12    volume and provided with an inlet tube carrying the  
13    mother liquor (ie. the liquid before processing) from a  
14    process vessel. The mother liquor in the inlet tube  
15    may, if desired, be raised to a sufficient pressure to  
16    cause filtrate to pass through a membrane in the cell  
17    into a filtrate chamber of minimal volume and from  
18    which chamber an outlet tube may be provided for  
19    returning the filtrate to the process vessel. The  
20    filtrate in the outlet tube may, if desired, be reduced  
21    in pressure by suction to produce the pressure  
22    differential required for filtration. The cell should  
23    additionally have a second outlet tube on the mother  
24    liquor side of the membrane so that the unfiltered  
25    residue of the mother liquor may be returned directly  
26    to the process vessel. The filtrate chamber may carry  
27    in close proximity to the membrane a sensor or an array  
28    of several sensors as well as a sampling port for the  
29    removal of samples for external analysis. Preferably  
30    the sensors may be bio-sensors, optical devices, pH  
31    probes, conductivity electrodes or any other devices  
32    for analysing the contents of the filtrate. The  
33    membranes may be of any of the known ceramic or  
34    polymeric micro- or ultra-filtration types in hollow  
35    fibre or flat membranes forms.

36



1 In one embodiment the device is a processing and  
2 handling system for liquids which controls, or removes  
3 suspended or dissolved particles and substances in a  
4 process liquor by filtration of the liquor through  
5 micro- or ultra-filtration membranes and which system  
6 may incorporate a direct sensor or plurality of sensors  
7 so that specific soluble substances can be analysed  
8 without interference with or contamination of the  
9 sensors. In the system, control of the process can be  
10 made rapidly by microprocessor or computer via a feed-  
11 back loop system.

12  
13 Thus the present invention provides a device for use as  
14 a liquid handling system, the device allowing a  
15 selective sample from a mother liquor to be taken,  
16 which sample is free or substantially free from  
17 substances of above or below a chosen particle or  
18 molecular size. Desirably the device totally contains  
19 all the fluids and materials being processed. The  
20 device comprises a flow-through cell containing a  
21 micro- or ultra-filtration membrane or a plurality of  
22 such membranes arranged for separating ingredients of  
23 differing particle or molecular size, and a filtrate  
24 chamber in which the filtrate collects.

25  
26 The flow-through cell may have provision for ingress of  
27 unfiltered liquor at higher positive or negative  
28 pressure.

29  
30 In another embodiment, a separating and sampling device  
31 for fluids is provided which is capable of taking a  
32 selective sample from a mother liquor, which sample is  
33 free or substantially free from substances of above a  
34 chosen particle or molecular size. The device  
35 comprises a flow-through cell containing a micro- or  
36 ultra-filtration membrane or a plurality of such

1 membranes arranged for cross-flow filtration. The  
2 device has a filtrate chamber in which the filtrate  
3 collects for examination. The cell has provision for  
4 ingress of unfiltered liquor at higher pressure and  
5 egress of filtered liquor at lower pressure. The  
6 membrane or membranes may be in the form of a sheet, of  
7 tube or of hollow fibres and may contain pores of sizes  
8 from 0.001 to 30 microns in diameter. The membranes  
9 may possess Molecular Weight cut-off values from 300 to  
10 1,000,000 Daltons. The filtrate chamber may  
11 incorporate a sensor or plurality of sensors that  
12 produce electrical signals in response to changes in  
13 the chemical composition of the fluid surrounding the  
14 sensor. The sensors may be biosensors. Optionally the  
15 device may be incorporated along with pumps and tubing  
16 into an apparatus arranged so that mother liquor may be  
17 continuously pumped through the device for separation  
18 and sampling. In such an apparatus there may be  
19 provision for returning the filtered liquor and/or  
20 filtrate to the mother liquor; and also the flow  
21 through the membrane may be reversed in direction so  
22 that gel polarisation may be eliminated or  
23 substantially eliminated thus increasing the working  
24 life of the cell.

25  
26 By way of example embodiments of the invention and uses  
27 therefor are shown in Figures 1-11.

28  
29 Figures 1 to 5 schematically illustrate various  
30 embodiments of the device according to the invention;

31  
32 Figure 6 is a perspective view of one embodiment of a  
33 device according to the invention, with a cut-away  
34 section to illustrate the membrane fibres;

35  
36 Figure 7 is a schematic diagram of a process circuit in

1 which the device according to the present invention can  
2 be used;

3  
4 Figures 8 and 9 are further schematic diagrams  
5 illustrating a device according to the present  
6 invention.

7  
8 Figures 10 and 11 illustrate two embodiments adapted to  
9 support cell growth and, optionally cellular challenge.

10

11 In more detail, Figure 1 shows the device indicated  
12 generally at 1 having a flat sheet membrane filter 2  
13 which separates the flow-through cell 3 from the  
14 filtrate chamber 4. Process liquor is pumped at  
15 pressure through the cell in the direction shown by the  
16 arrow and the filtrate may leave the filtrate chamber 4  
17 by a port 5 which may be fitted with a tap (not shown).  
18 Alternatively a further fluid may be input via port 5  
19 and be filtered across membrane 2. An agent may be  
20 located on the membrane filter 2, cell 3 and/or in  
21 chamber 4.

22

23 Figure 2 illustrates a device similar to that shown in  
24 Figure 1 and described above. In the device of Figure  
25 2 (shown generally at 1) the filter membrane 2 is in  
26 the form of a tube 6. The mother liquor is passed  
27 through the lumen of tube 6 (which forms flow-through  
28 cell 3), preferably at a controlled pressure, in the  
29 direction of the arrow. The filtrate will collect in  
30 chamber 4 and may be taken off via port 5 which again  
31 may if desired be fitted with a tap. Alternatively  
32 port 5 may be used to input a second fluid, either to  
33 react with the filtrate of the mother liquor (ie the  
34 agent may be present in the second fluid) or to control  
35 the pressure within the device.

36

1 Figure 3 illustrates a further embodiment, similar to  
2 those previously described with respect to Figures 1  
3 and 2. In the embodiment of Figure 3 the membrane  
4 filter (shown generally at 2) is in the form of hollow  
5 fibre membranes 7 of which two are illustrated for  
6 simplicity. The number of hollow fibre membranes may  
7 be adjusted from 1 to several hundred depending upon  
8 the size of the device. The lumen of the individual  
9 fibres are used to transport the mother liquor into the  
10 device and thus act as the flow-through cell. The  
11 filtrate collects in chamber 4. The ends of the hollow  
12 fibres are sealed into the device to prevent the mother  
13 liquor entering the filtrate chamber 4 by any means  
14 other than by passing across the membrane.  
15

16 Figure 4 depicts a further embodiment of device 1 with  
17 tubular filter membrane 2 as depicted in Figure 2 but  
18 with the addition of a direct sensor 8. The sensor 8  
19 may be, for example, a pH sensor, a conductivity sensor  
20 or a biosensor. In use the component of interest  
21 passes across the membrane filter 2 into the filtrate  
22 chamber 4. The pressure differential across the  
23 membrane may be controlled via port 5 which may contain  
24 a tap or valve. The component of interest may react  
25 with or otherwise be detected by sensor 8 which then  
26 generates production of an output signal, preferably an  
27 electrical, audible or visual output signal.  
28

29 Figure 5 illustrate three further embodiments of a  
30 device according to the present invention. In general  
31 the embodiments shown are similar to those described  
32 above for Figures 1 to 4, especially Figure 3. In  
33 Figure 5A, the membrane 2 consists of a single hollow  
34 fibre membrane, having an internal lumen of  
35 approximately 1mm. The whole of the volume between the  
36 exterior surface of the membrane and the interior

1 surface of the outer casing 9 is filled with a material  
2 11, such as LCM 32 or LCM 35 from Ablestick, which  
3 contains an agent able to react with a component of  
4 interest in the mother liquor. In use the mother  
5 liquor is passed down the lumen of the hollow fibre  
6 membrane 7 and filtrate moves across the membrane  
7 surface by cross-flow filtration. The component of  
8 interest present in the filtrate then encounters the  
9 agent held within the material 11. In the illustrated  
10 embodiment the material is solid and the agent is  
11 uniformly distributed therein. However a porous  
12 material encapsulating the agent could equally be used.  
13 The component may either be modified by reacting with  
14 the agent or may be simply detected by the agent which  
15 may not alter it physically or chemically. For example  
16 the agent could be light emitting, photosensitive or  
17 photoreactive.

18  
19 In Figure 5B the material 11 does not entirely fill the  
20 volume between the exterior surface of the membrane and  
21 the interior surface of the outer casing 9, but leaves  
22 a pre-determined volume able to accept filtrate. The  
23 agent may be present either in the free volume or else  
24 be held within material 11 as described for Figure 5A  
25 above. Alternatively two different agents may be  
26 present in these separate physical locations.

27  
28 Although not illustrated, the device of Figure 5B could  
29 also be produced having two or more (for example three,  
30 four or five) volumes separately filled with material  
31 11 (or with different types of material 11) and  
32 separated or abutting each other. Again different  
33 agents or different concentrations of agents could be  
34 contained in each.

35  
36 In Figure 5C, the device is as shown in Figure 5B,

1 except that the device further includes a additional  
2 port 5. Port 5 may be used to draw off filtrate, to  
3 introduce a second fluid, optionally containing an  
4 agent to modify or detect the component of interest or  
5 simply to adjust the pressure and thus the flow across  
6 the membrane.

7  
8 In Figure 6, device 1 is fitted with a membrane filter  
9 2 which separates the flow-through cell 3 from the  
10 filtrate chamber 4. Process liquor is pumped by pump  
11 17 at positive or negative pressure through the device  
12 1 in the direction shown by the arrow. The filtrate  
13 leaves the filtrate chamber 4 by a port 5 and is sensed  
14 by a direct sensor 8, for example a pH sensor, a  
15 conductivity sensor or a biosensor. Excess unfiltered  
16 fluid exits via port 10. In the device illustrated  
17 part of the outer casing is absent in order to  
18 illustrate the membrane filter 2 used which is shown to  
19 consist of multiple hollow fibres 7 as in Figure 3.  
20 However other forms of membrane filters 2 can also be  
21 used.

22  
23 Figure 7 shows a process vessel 12 in which cells are  
24 being cultured under agitation using stirrer 30 and in  
25 which the glucose concentration requires to be  
26 continuously monitored. A peristaltic pump 17 pumps  
27 the mother liquor from the vessel to an inlet port 13  
28 in a device 1 according to the present invention. The  
29 device illustrated is that shown in Figure 6, but any  
30 of the other embodiments could likewise be used. Pump  
31 17 maintains sufficient pressure to cause filtration  
32 through a hollow fibre membrane filter 2. Within the  
33 filter cell is a glucose bio-sensor 8 which measures  
34 the quantity of glucose in the filtrate and the  
35 filtrate may be returned to the process vessel through  
36 outlet tube 14 and the residual unfiltered liquor may

1 be returned to the process vessel through outlet tube  
2 15.

3  
4 Figure 8 shows the filter cell incorporated in a  
5 working system in which the process liquor is passed by  
6 a pump 17 through a pressure sensor 20 to the device  
7 according to the invention 1, fitted with a direct  
8 sensor 8 which is monitored by a direct sensor assay  
9 instrument 16. The process liquor exits from the  
10 device 1 through a second pressure sensor 20a and a  
11 second pump 17a which is adjusted in pumping rate  
12 relative to the pumping speed of the first pump 17 to  
13 control the pressure in the device 1. Filtrate  
14 accumulates in the filtrate chamber 4 (not shown) and  
15 is pumped from it by the third pump 17b by way of a  
16 third pressure sensor 20b. The process liquor is  
17 returned to the process via connecting tubes (not  
18 shown) and the filtrate is directed through a multi-  
19 port valve 18 to an external analytical system 19 for  
20 further analysis, or to a drain or filtrate store 21,  
21 or to a filtrate return line 22 in which it may join  
22 the sampled process liquor returning to the process.

23  
24 Figure 9 shows the device 1 according to the invention  
25 incorporated in a working system in which the process  
26 liquor is passed by a pump 17 through a pressure sensor  
27 20 to the filter cell 1, fitted with a direct sensor 8  
28 which is monitored by a direct sensor assay instrument  
29 16 which can be microprocessor or computer controlled.  
30 The process liquor exits from the device 1 through a  
31 second pressure sensor 20a and a second pump 17a which  
32 is adjusted in pumping rate relative to the pumping  
33 rate of the first pump 17 to control the pressure in  
34 the device 1. Filtrate accumulates in the filtrate  
35 chamber 4 (not shown) and is pumped from it by the  
36 third pump 17b by way of a third pressure sensor 20b.

1 Within the enclosed circuit of pumps 17, 17a and 17b  
2 and pressure sensors 20, 20a and 20b processing of  
3 material within the device 1 can be achieved at above  
4 and below atmospheric pressure on both sides of the  
5 membrane 2 (not shown). The process liquor is returned  
6 to the process and the filtrate is directed through a  
7 multi-port valve or valves 18 to an external analytical  
8 system 19 for further analysis, or to drain or filtrate  
9 store 21 or to a filtrate return line 22 in which it  
10 may join the sampled process liquor returning to the  
11 process. If the process involves cell culture, at the  
12 end of the process, mature cells or cells ready for  
13 harvest can be flushed out of the circuit and collected  
14 via line to container 23. This can be achieved  
15 continuously or in discreet batches. The whole system  
16 is constructed of materials that can be sterilised.

17

18 An additional sampling circuit is illustrated whereby a  
19 sample can be withdrawn to testing unit 24 and can  
20 either be held in test 25 or returned via pump 17c to  
21 the process circuit. Testing unit 24 may be an  
22 additional sensor and assay instrument. Alternatively  
23 unit 24 may be used to incorporate a substance to the  
24 process liquor.

25

26 2Figure 10 shows a device according to the invention  
27 shown generally at 1, the membrane filter lumen being  
28 shown in dotted lines. In the embodiment shown pump 17  
29 pushes cell growth medium around a closed loop made up  
30 of line 26 and device 1. Present in line 26 is an  
31 outlet means (generally a tap or valve) 27, a sensor 8  
32 and also injection or withdrawal means (here  
33 illustrated as syringes, but the invention is not so  
34 limited) 28a and 28b. The injection or withdrawal  
35 means 28a and 28b may be used either to introduce  
36 factors exhausted from the medium due to cell growth or



1 may take a sample of the medium from the closed loop  
2 for analysis. This latter option may be of interest  
3 where the cells grown on the medium are producing a  
4 factor or substance which is of interest.

5  
6 Multiple devices 1 according to the invention may be  
7 incorporated into a single closed loop arrangement as  
8 is shown in Figure 11. The system may be under the  
9 control of microprocessor or computer 35. Multiple  
10 injection or withdrawal means 28 (illustrated as  
11 syringes) are selectively connectible to individual  
12 devices 1 by valves 29 in lines 26. The devices can be  
13 connected to biosensors 8 and a line 32 including a  
14 pressure sensor 33 and a displacement pump 34 can be  
15 used to adjust pressure in the circuit. Collection  
16 bays 31 can be provided at various locations for  
17 collection of filtrate or mother liquor from specific  
18 device, as required. The precise layout of any  
19 particular system can be different from that  
20 illustrated.  
21

1     CLAIMS

2

3     1.    A device to process a fluid, the device having a  
4            membrane filter, wherein an agent able to detect  
5            or cause modification of at least one component of  
6            said fluid is localised in said device.

7

8     2.    A device according to Claim 1 wherein said agent  
9            is localised on said membrane filter.

10

11    3.    A device according to either one of Claims 1 and 2  
12            wherein filtration of the fluid occurs by cross-  
13            filtration.

14

15    4.    A device according to any one of Claims 1 to 3  
16            wherein the device further comprises a sensor.

17

18    5.    A device according to any one of Claims 1 to 4  
19            wherein the membrane filter is a single hollow  
20            fibre or multiple hollow fibres.

21

22    6.    A device according to Claim 5 wherein the membrane  
23            filter is a single hollow fibre.

24

25    7.    A device according to any one of Claims 1 to 6  
26            wherein the volume between one surface of a  
27            membrane and its boundary is at least partially  
28            filled with a porous substance.

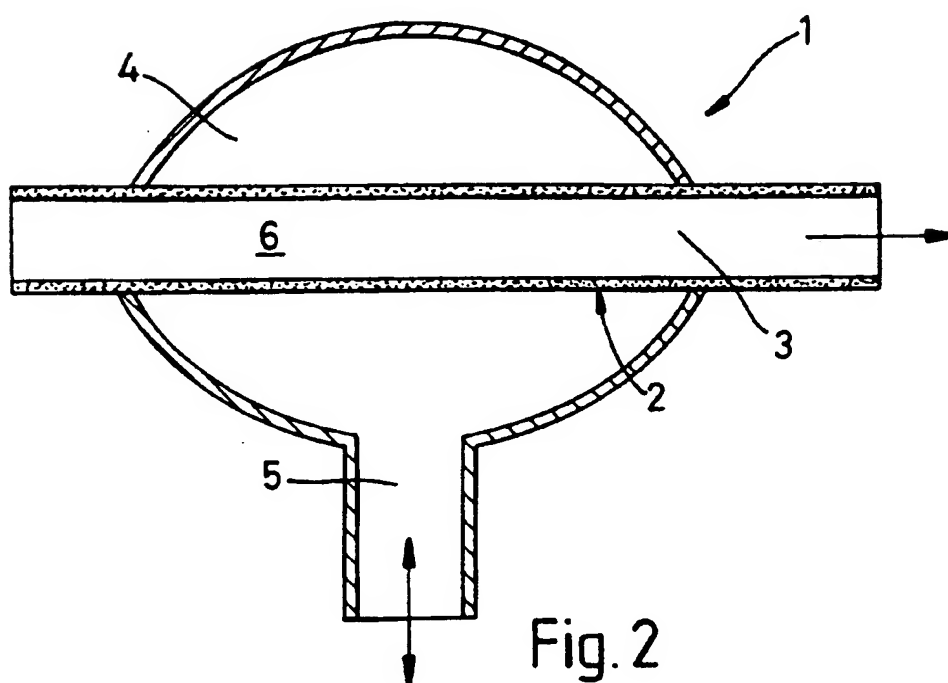
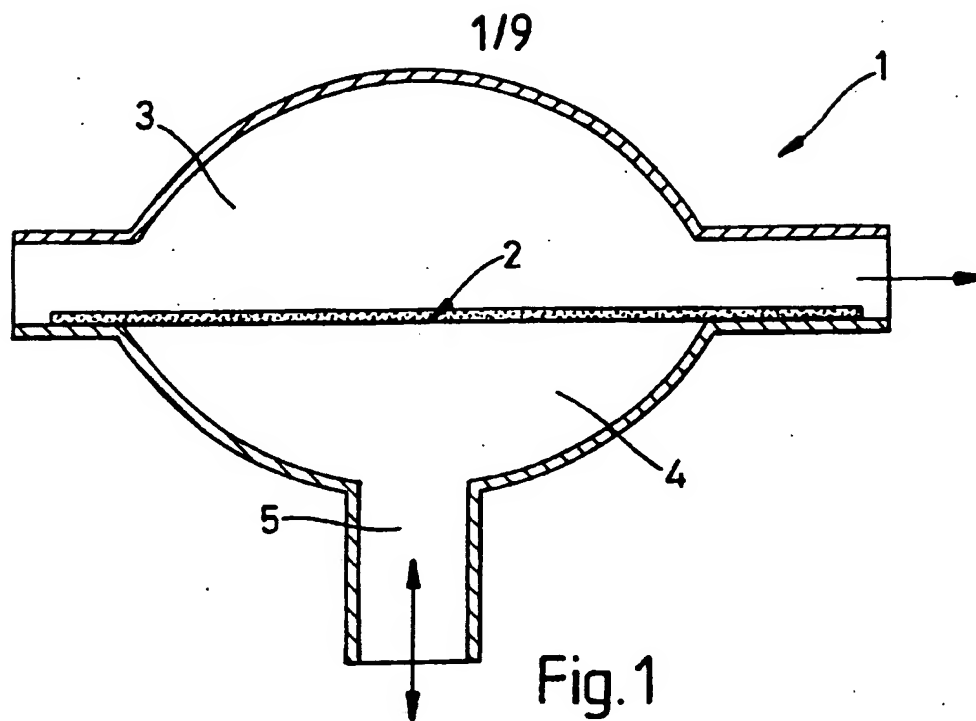
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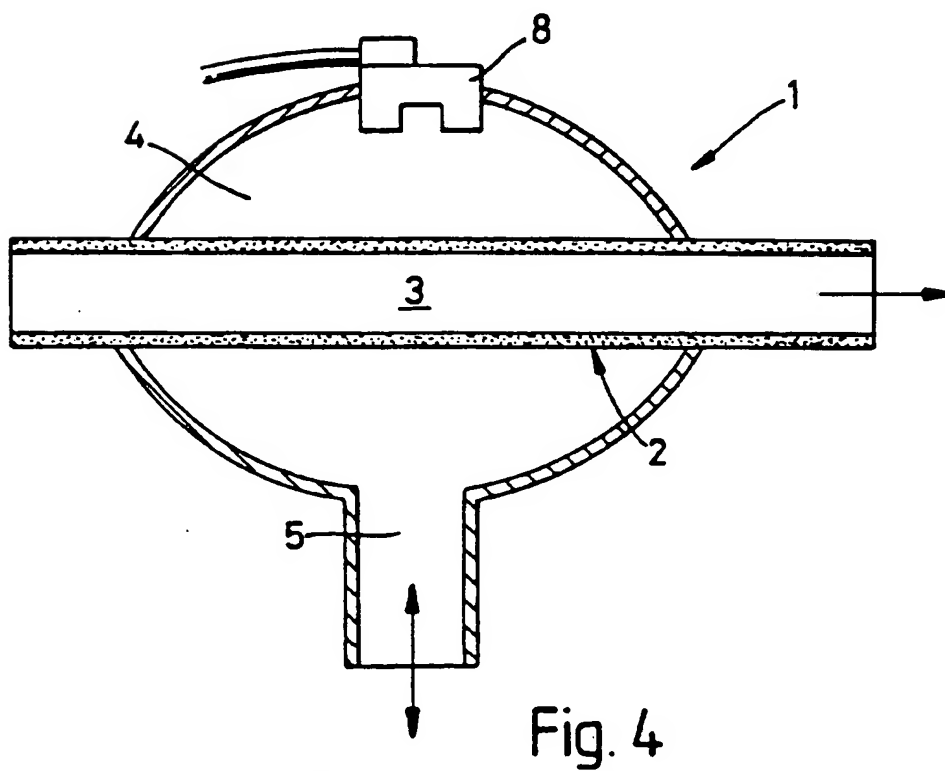
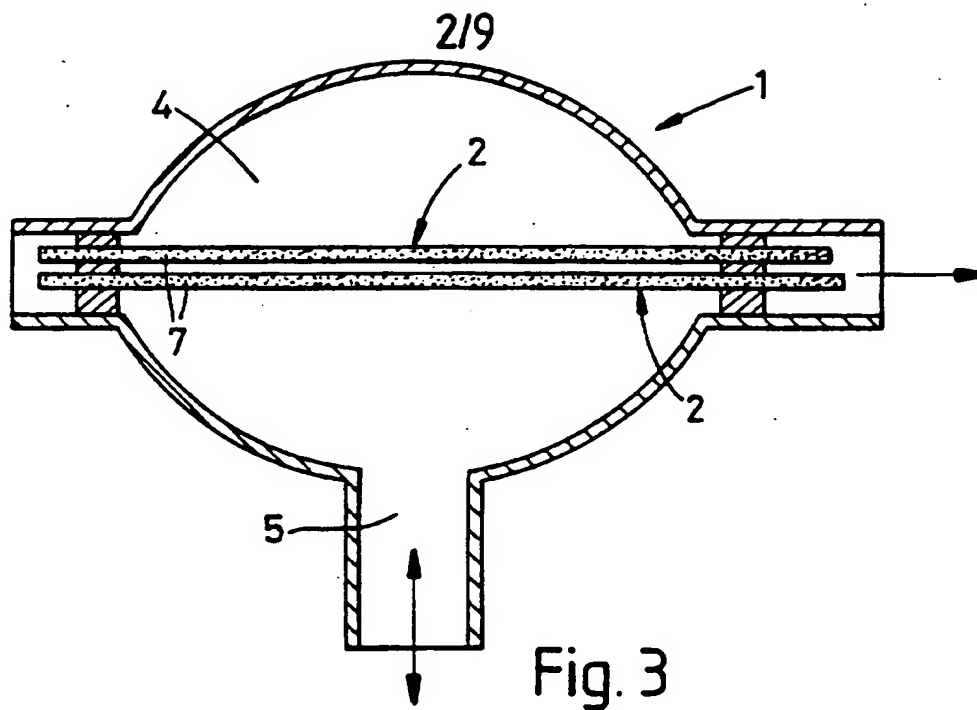
30    8.    A device according to Claim 7 wherein the porous  
31            substance contains said agent.

32

33    9.    A device according to any one of Claims 1 to 8  
34            wherein the agent is an enzyme, antibody, abzyme,  
35            a microbe, genetic material, lectin, a chemical  
36            reagent, a catalyst, or a function part or any

- 1 combination thereof.
- 2
- 3 10. A process of detecting or modifying a component of
- 4 a liquid substrate, wherein:
- 5
- 6 a. said liquid substrate is filtered by cross-
- 7 flow filtration through a device as claimed
- 8 in any one of Claims 1 to 9, the component
- 9 being present in the filtrate; and
- 10
- 11 b. the filtered component is detected or
- 12 modified by an agent located on a filter in
- 13 said device.
- 14
- 15 11. A process as claimed in Claim 10 wherein the agent
- 16 is a cell culture and said component is a nutrient
- 17 required for cell growth.
- 18
- 19 12. A process as claimed in Claim 10 wherein the
- 20 liquid substrate is a waste product and said agent
- 21 detects or renders harmless an undesirable
- 22 component of said waste product.
- 23
- 24 13. A process as claimed in Claim 10 wherein the
- 25 liquid substrate is or comprises a biological
- 26 sample and said agent detects a component of said
- 27 sample.
- 28
- 29 14. A method of diagnosis, said method comprising
- 30 subjecting a test liquid comprising a biological
- 31 sample from a patient to a process as claimed in
- 32 Claim 10, wherein said agent is able to
- 33 selectively detect the presence and/or amount of
- 34 component within said liquid.





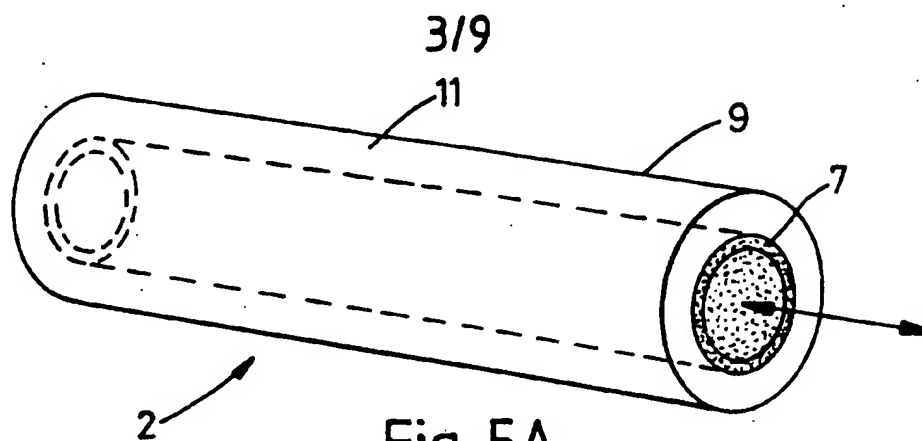


Fig. 5A

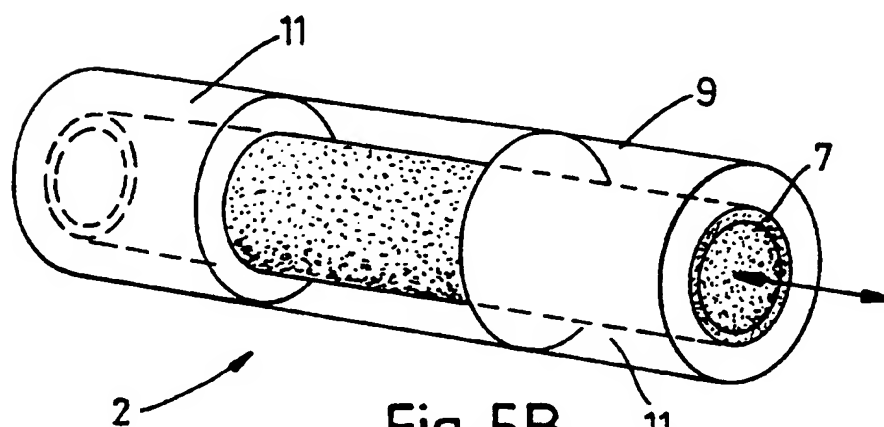


Fig. 5B

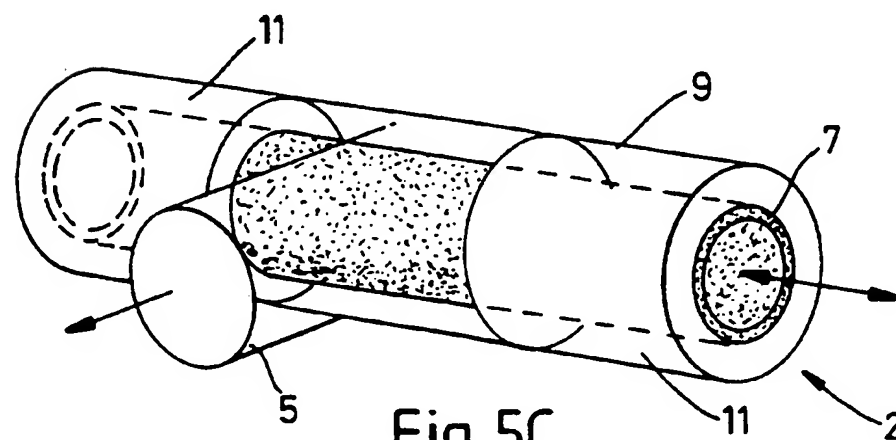
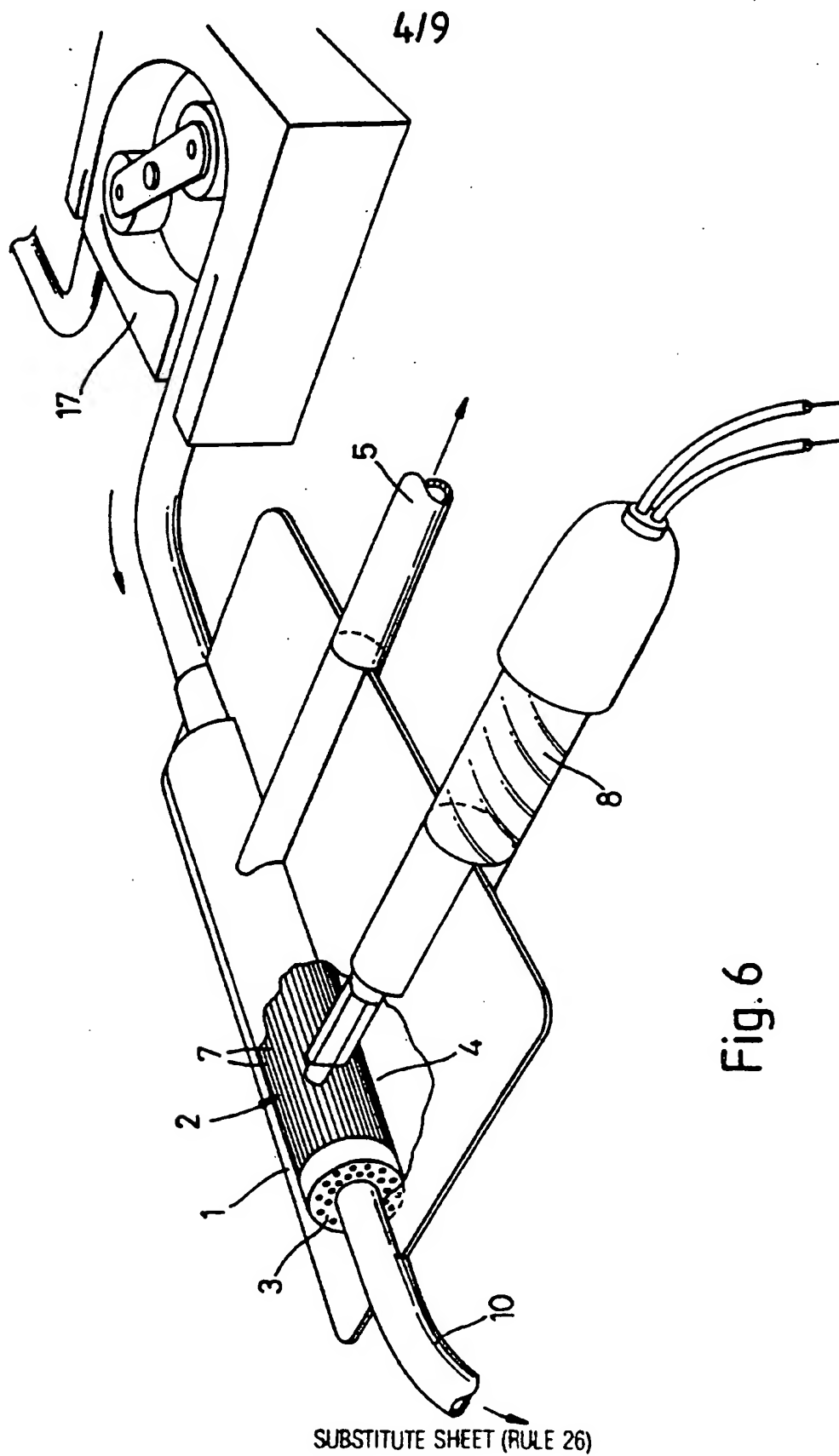


Fig. 5C



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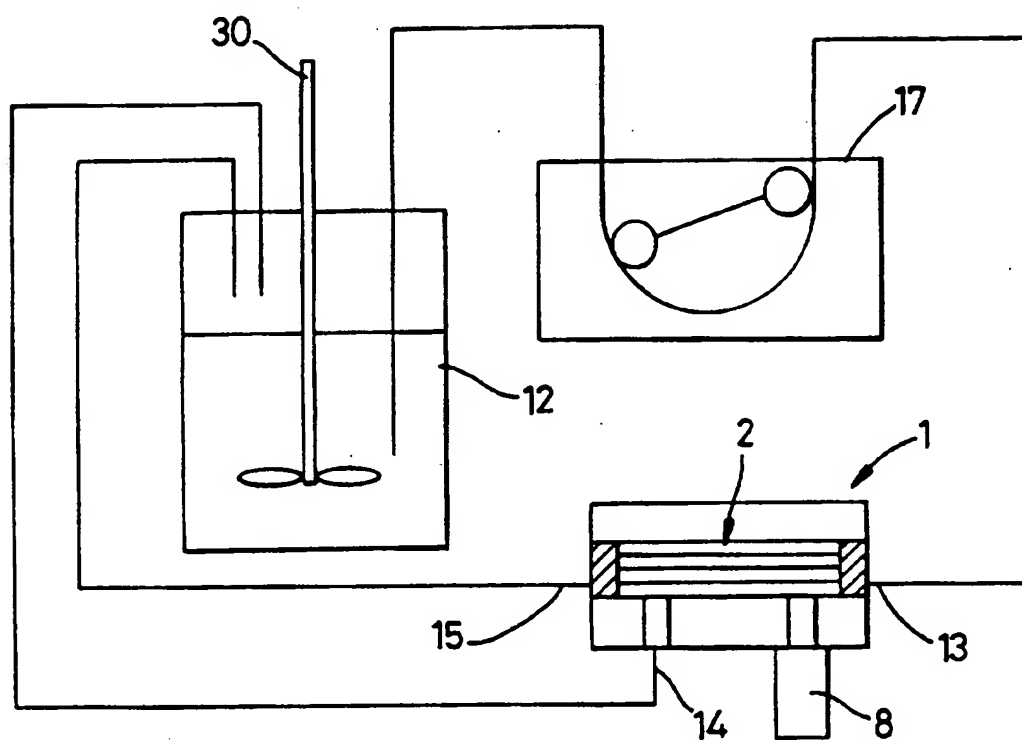


Fig. 7



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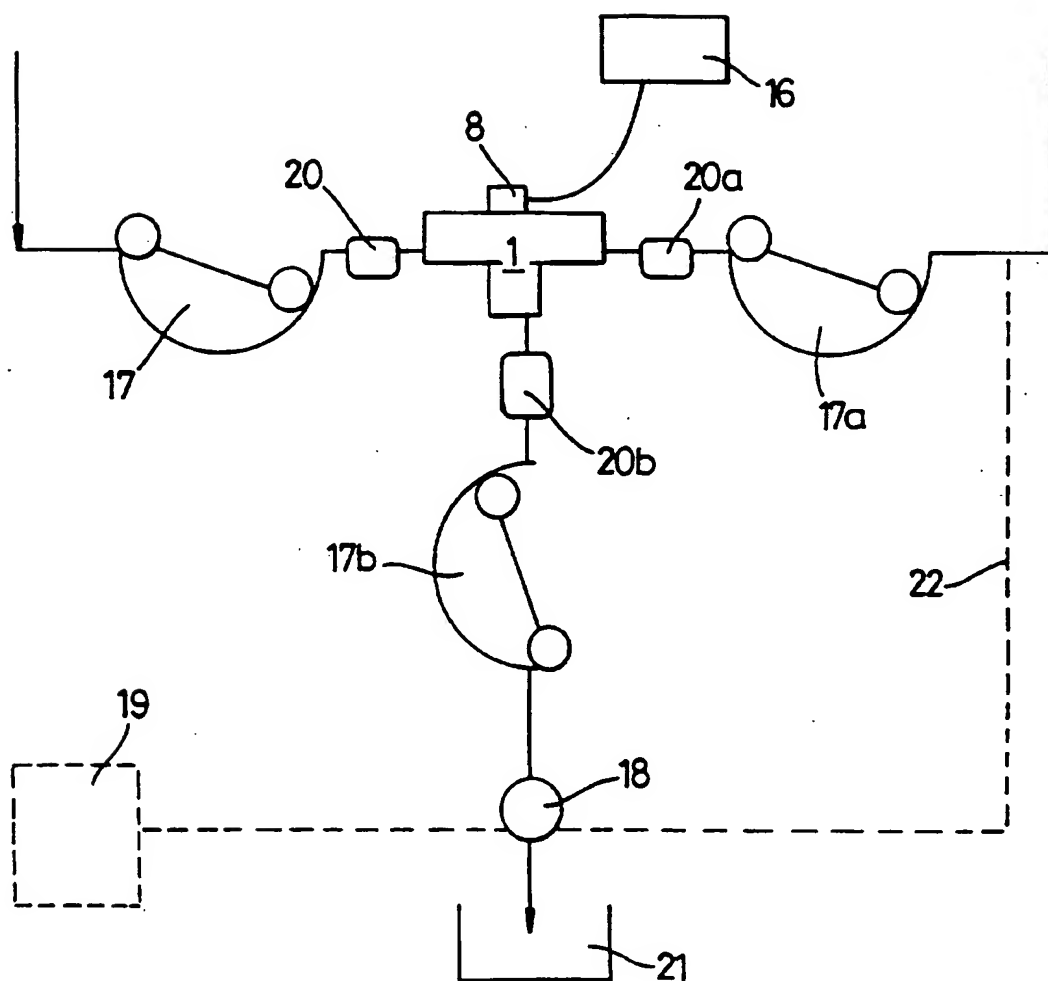


Fig. 8

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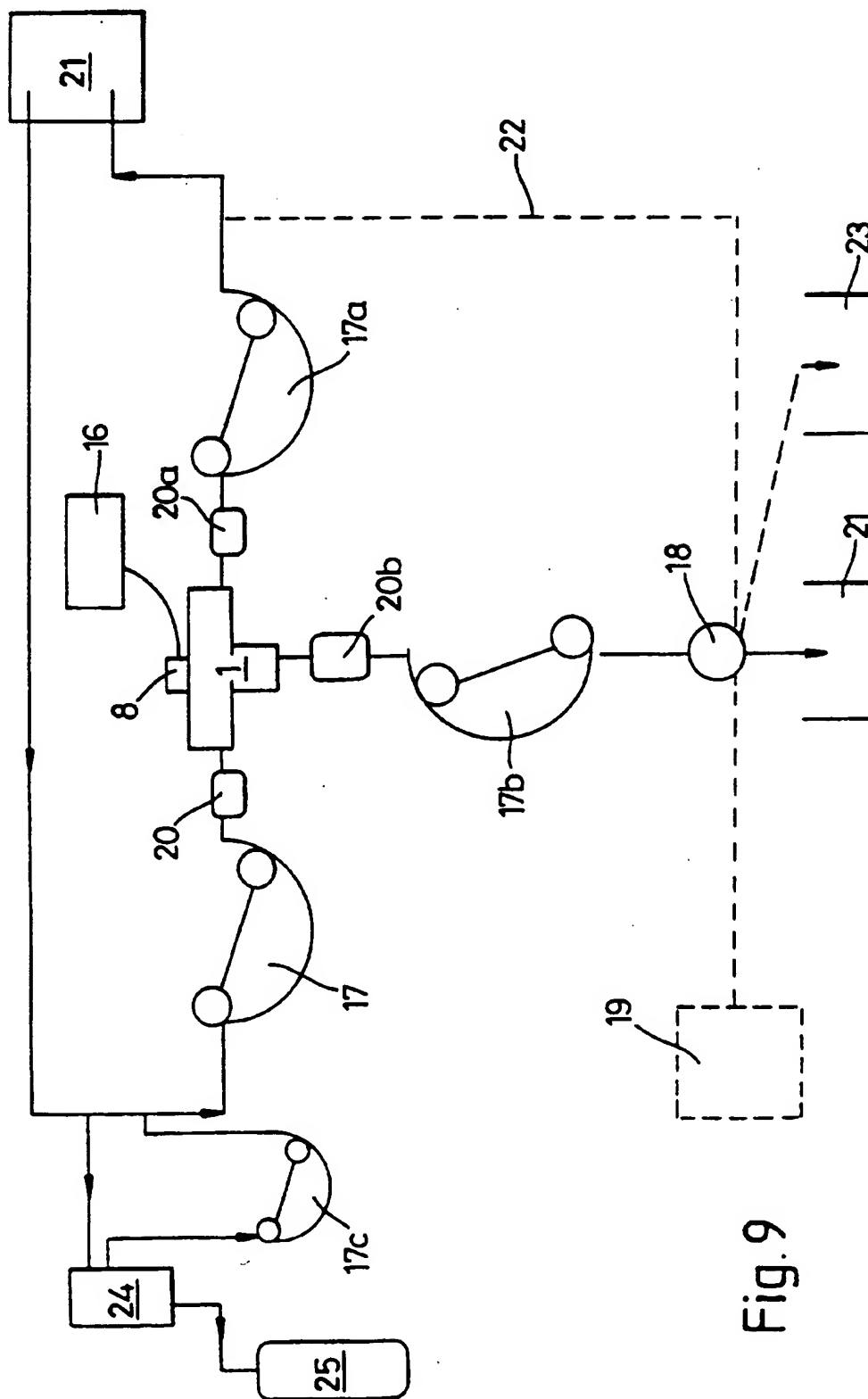
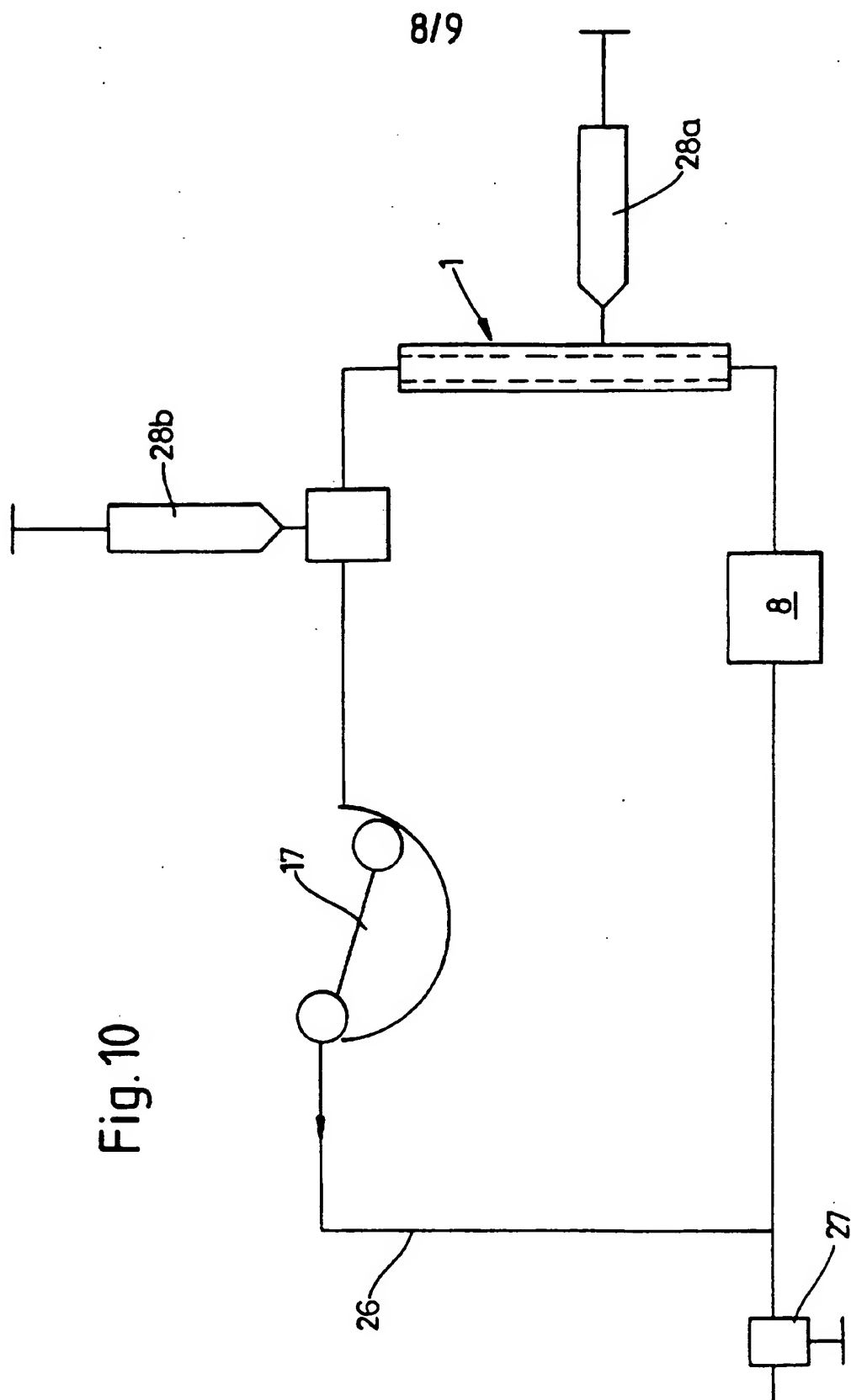


Fig. 9



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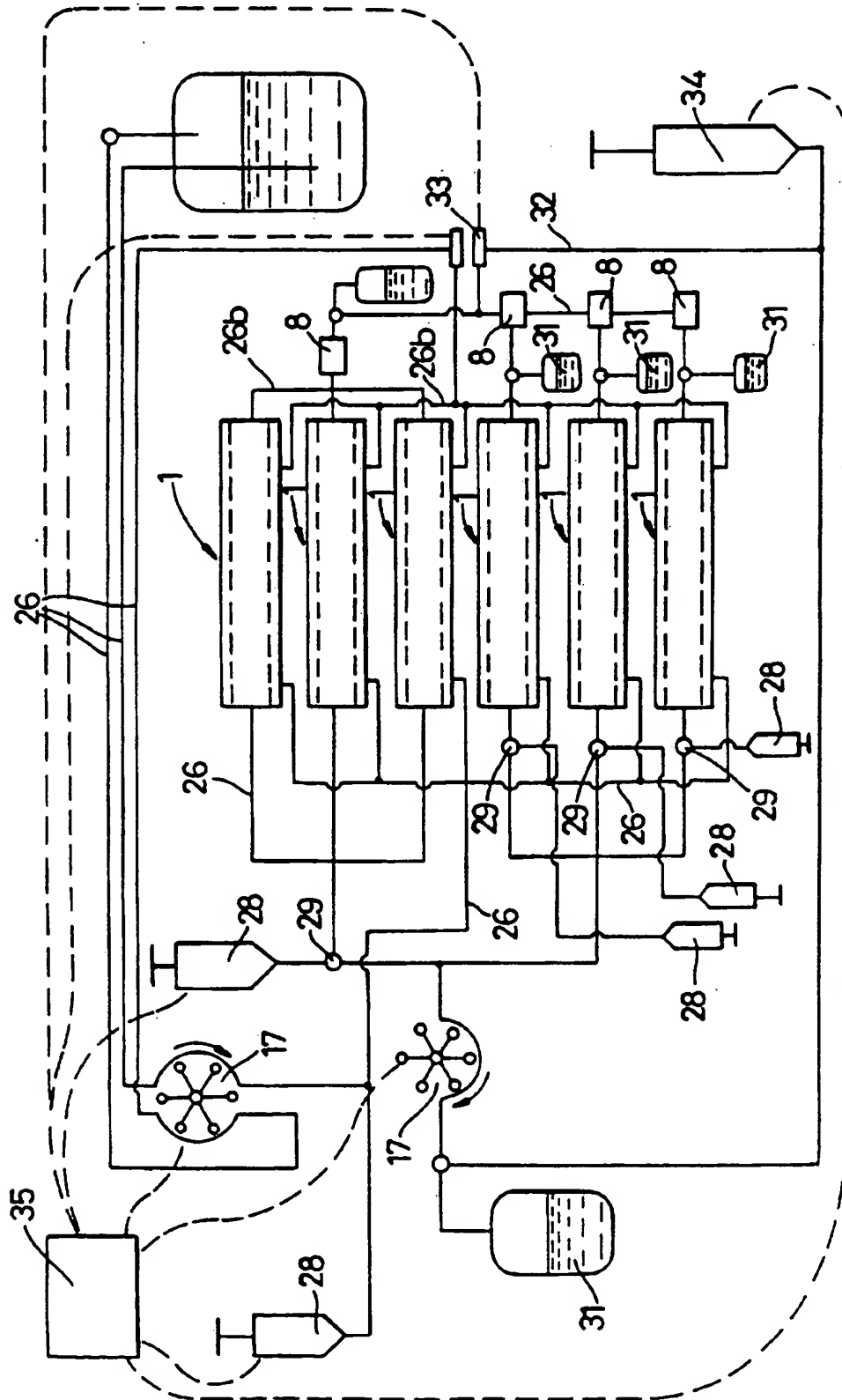


Fig.11

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 95/01834

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 B01D61/00 G01N33/48

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 B01D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 685 463 (R. B. WILLIAMS) 11 August 1987 see the whole document ---	1,3-6,9, 10,13,14
X	US,A,4 311 789 (U. T. G. NYLEN ET AL.) 19 January 1982 see the whole document ---	1,3-10, 13,14
X	FR,A,2 640 643 (L'OREAL) 22 June 1990 see the whole document ---	1-4,9, 10,13,14
X	WO,A,93 06045 (IMPERIAL COLLEGE OF SCIENCE, TECHNOLOGY & MEDICINE) 1 April 1993 see the whole document ---	1-3,9, 10,12
-/--		

☒ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

28 November 1995

Date of mailing of the international search report

01-12-1995

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# INTERNATIONAL SEARCH REPORT

national Application No  
PCT/GB 95/01834

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 120 285 (NIPPON OIL AND FATS CO, LTD) 3 October 1984 see the whole document ---	1,3,5,9, 10
X	WO,A,87 02381 (SEPRACOR, INC.) 23 April 1987 see the whole document ---	1,3,5-10
X	EP,A,0 541 245 (EXXON RESEARCH AND ENGINEERING CO) 12 May 1993 see the whole document ---	1-3,9,10
X	EP,A,0 228 885 (NGK INSULATORS, LTD.) 15 July 1987 see the whole document ---	1,3,9,10
X	EP,A,0 155 237 (MBR BIO REACTOR AG) 18 September 1985 see the whole document ---	1,3,4, 7-11
P,X	WO,A,94 16800 (TYGOLA PTY. LTD.) 4 August 1994 see the whole document ---	1,9
A	GB,A,2 252 260 (MEDICAL RESEARCH INTERNATIONAL) 5 August 1992 see the whole document -----	1,7

# INTERNATIONAL SEARCH REPORT

Information on patent family members

National Application No

PCT/GB 95/01834

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4685463	11-08-87	NONE	
US-A-4311789	19-01-82	SE-B- 396819	03-10-77
		AT-B- 361131	25-02-81
		AU-B- 504818	01-11-79
		AU-B- 2101176	06-07-78
		BE-A- 850006	15-04-77
		CA-A- 1075136	08-04-80
		CH-A- 631546	13-08-82
		DE-A- 2658101	14-07-77
		FR-A, B 2337341	29-07-77
		GB-A- 1581353	10-12-80
		JP-A- 52085885	16-07-77
		NL-A- 7614448	04-07-77
		SE-A- 7600024	02-07-77
		US-A- 4229542	21-10-80
FR-A-2640643	22-06-90	CA-A- 2005624	16-06-90
		DE-T- 68907197	20-01-94
		EP-A, B 0384090	29-08-90
		JP-A- 3103224	30-04-91
		US-A- 5250419	05-10-93
WO-A-9306045	01-04-93	AU-A- 2588592	27-04-93
		CA-A- 2119383	01-04-93
		EP-A- 0604514	06-07-94
		JP-T- 6510696	01-12-94
EP-A-120285	03-10-84	JP-C- 1844457	25-05-94
		JP-A- 59154999	04-09-84
		DE-A- 3485748	02-07-92
		US-A- 5024942	18-06-91
WO-A-8702381	23-04-87	US-A- 4795704	03-01-89
		AU-B- 597284	31-05-90
		AU-B- 6473986	05-05-87
		CA-A- 1289493	24-09-91
		DE-A- 3688908	23-09-93
		DE-T- 3688908	20-01-94
		EP-A, B 0243404	04-11-87

# INTERNATIONAL SEARCH REPORT

Information on patent family members

National Application No

PCT/GB 95/01834

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-8702381		JP-T- 63501612 KR-B- 9405577 SU-A- 1787044	23-06-88 21-06-94 07-01-93
EP-A-541245	12-05-93	US-A- 5210059 CA-A- 2078973 JP-A- 5237395	11-05-93 11-04-93 17-09-93
EP-A-228885	15-07-87	JP-C- 1766147 JP-B- 4051211 JP-A- 62160121 DE-D- 3650155 DE-T- 3650155 US-A- 4865630	11-06-93 18-08-92 16-07-87 12-01-95 06-04-95 12-09-89
EP-A-155237	18-09-85	DE-A- 3409501 JP-A- 60210982	24-10-85 23-10-85
WO-A-9416800	04-08-94	AU-B- 5966394	15-08-94
GB-A-2252260	05-08-92	NONE	